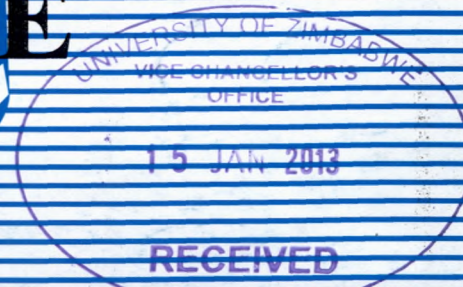
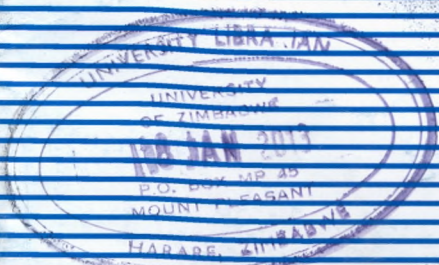


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# THE CENTRAL AFRICAN JOURNAL OF MEDICINE

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## ORIGINAL ARTICLES

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### Inappropriate use of Promethazine and Promethazine-containing products in children under the age of three years in Harare, Zimbabwe

\*A MARUME, \*TG MUVIRIMI, \*\*K CHITINDINGU, \*I MUTINGWENDE

#### Abstract

**Objectives:** To determine whether there was inappropriate use of promethazine, Stopayne® or Goldgesic® in children under three (3) years of age in Harare, and to measure its extent. *Inappropriate* referred to administering these medicines to children under the age of two (2) years for any indication or the administering of these medicines to an otherwise healthy child less than three (3) years old for sedation purposes.

**Design:** A descriptive cross-sectional study carried out between May and July 2010.

**Setting:** Retail pharmacies in Harare, Zimbabwe.

**Results:** The percentages of pharmacy personnel who indicated that parents request these syrups for sedation purposes in their children were: 20.8% promethazine; 18.9% Stopayne®; and 9.6% Goldgesic®. With respect to parents, it was found that 25% administered these syrups to children aged below 2 years. Of the parents who administered these syrups to their children about 7.7% did so for sedation purposes.

**Conclusion:** There was significant inappropriate use of all 3 syrups in children under the age of 3 years ( $p < 0.05$ ). Direct evidence was seen in that pharmacy personnel dispensed these medicines for use in infants and parents administered these syrups to infants.

*Cent Afr J Med 2011;57(9/12):39-43*

#### Introduction

In Zimbabwe, promethazine, Stopayne® and Goldgesic® syrups are classified as pharmacy drugs (P) by the Medicines Control Authority of Zimbabwe (MCAZ). A pharmacy drug, according to the Medicines and Allied Substances Control Act (1991),<sup>8</sup> is a medicine that is to be sold only, by a pharmacist, any person under the continuous personal supervision of a pharmacist, from licensed pharmacies or by a wholesale dealer with a valid wholesale dealer's permit. Promethazine, Stopayne® and Goldgesic® syrups are available over-the-counter (OTC), without need for a prescription.

Promethazine (Phenergan®) is available in various

dosage forms, but is mostly dispensed for children as a syrup containing 5mg of promethazine hydrochloride per 5mL of the medicine. This drug is indicated for symptomatic relief of allergy such as hay fever and urticaria, for premedication, emergency treatment of anaphylactic reactions, and motion sickness.<sup>9</sup> The British National Formulary, however, does not recommend the use of hypnotics/ sedatives in children. Promethazine exerts its anti-histamine effects through blockade of histamine ( $H_1$ ) receptors, which are distributed in the brain, smooth muscle, heart as well as capillary endothelium.

The syrups have alcohol in their formulations, with Goldgesic® having 12.5% (m/v) and Stopayne® having of 10% (m/v). Goldgesic® and Stopayne® are indicated

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for the relief of mild to moderate pain associated with fever. Paracetamol is a centrally acting analgesic and is also an anti-pyretic. Codeine is also a centrally acting analgesic and it exerts its effects through opioid receptor stimulation in the brain and spinal cord.<sup>9</sup>

The over-the-counter availability of these preparations may promote the perception that they are safe. However, promethazine use is not recommended for children younger than the age of 2 years, whilst codeine is not recommended for infants under the age of 1 year.<sup>9</sup>

The adverse effects reported with promethazine use in children include respiratory depression, cardiac arrest, sleep apnoea and seizures.<sup>1</sup> The relative immaturity of drug metabolising enzyme systems in young children is a factor that may increase the adverse effects of drugs such as promethazine and codeine, especially in children younger than 6 months. In addition, alteration of hepatic enzymes by illnesses or concurrent drug therapy (such as paracetamol) may further alter metabolism of a drug such as codeine, and increase the risk of an adverse reaction because of accumulation of the drug. The impact of these adverse reactions would be minimal if parents administered these over-the-counter medications only for appropriate indications and only in children over 2 years of age.

Administration of promethazine to infants less than two years of age carries a grave health risk. Promethazine has been implicated in Sudden Infant Death Syndrome (SIDS)<sup>6</sup> and in the generation of sleep apnoeas in normal infants (Khan, 1982).

A study carried out in Harare showed 70% of OTC staff had little knowledge about the toxicity of promethazine. In light of the findings of these studies, it was therefore, important to determine pharmacy staff dispensing practices with regard to promethazine and the other promethazine-containing preparations. Research into inappropriate use of these medicines had not been done before in Zimbabwe. The findings from studies carried out in other countries could not simply be extrapolated to Zimbabwe because common knowledge, attitudes and perceptions of people may vary from one country to another.<sup>1,2,3</sup> The results of this study might stimulate research in areas related to this subject consequently the category of distribution of preparations with promethazine might be changed by MCAZ into either pharmacist initiated medicines (PIMs) or prescription preparations. According to the Medicines and Allied Substances Control Act Statutory Instrument 150, PIMs were medicines that did not require a medical practitioner's prescription, but might only be supplied on the recommendation of a pharmacist who showed maintain proper records relating thereto.

## Materials and Methods

This was a cross sectional study carried out between

May and July 2010 in Harare, Zimbabwe. Information obtained from the Medicines Control of Authority of Zimbabwe (MCAZ) states that there are 152 retail/community pharmacies in Harare as of May 2010. The study population was taken from pharmacies in Harare, and included all of the following pharmacy personnel: pharmacists, pharmacy technicians, dispensary assistants, over the counter (OTC) assistants and parents, child care-givers with children 3 years old and younger who would have visited the pharmacy during the research period.

Use of promethazine-containing syrups was investigated in children 3 years old and younger in an attempt to determine whether these medicines were being given to children for real or perceived hyperactivity. Hyperactivity was more perceivable in an older child than in a young infant hence 3 years of age was the chosen upper limit. Some signs of hyperactivity included inability to focus, excessive talking, inability to relax, and temper tantrums. The average age of children in the study was 16 months (standard deviation 9.9 months, median 16 months).

## Ethical Approval

Ethical approval for this study was sought from the Joint Parirenyatwa Hospital and College of Health Sciences Research Ethics Committee. Participants' confidentiality was maintained.

## Statistics

Sample sizes were calculated using Pocock's formula (Rosner, 2000). Minimum required sample size of parents or childcare-givers was determined as 960, given that the prevalence of inappropriate use 50%, significance level 5% and 10% margin of error.

The minimum required sample size of pharmacy personnel to be interviewed was determined as 530, given probability of having little knowledge 70%, 5% significance level, population size of 152 pharmacies (MCAZ list of licensed premises, 2010).

Sample sizes were calculated using the following equation that incorporated the total population:

$$n = \frac{N \times Z_{\alpha/2}^2 \times p(1-p)}{d^2(N-1) + Z_{\alpha/2}^2 p(1-p)}$$

Where  $n$ = sample size,  $p$ =probability of obtaining the outcome of interest  $Z_{\alpha/2}^2$  = the z-score for a 5% significance level (1.96),  $d$ = the desired interval= 0.123,  $N$ =total population.

Two different interviewer-administered questionnaires were used to obtain data from exit parents or caregivers of retail/community pharmacies in Harare, and the other to obtain information from pharmacy personnel. Exit parents or caregivers of retail/community

pharmacies in Harare and the pharmacy personnel were conveniently selected from all the 152 pharmacies in Harare. The questionnaires incorporated both close-ended and open-ended questions. Demographic questions included sex, number of years in practice (for pharmacy staff only) and profession. The rest of the questions were meant to assess knowledge and practices pertaining to use of promethazine, Stopayne® and Goldgesic® syrups.

Data were checked for completeness and consistency, before being computed and analysed using the software package Epi-info®. The  $\chi^2$  test was then used to determine the significance of any association between certain categorical values. The P-value used was 0.05.

## Results

Five hundred and thirty pharmacy personnel took part in this study: 190 (35.8%) pharmacists, 105 (19.8%) pharmacy technicians and 235 (44.4%) pharmacy assistants. The average number of years in practice was 5.5 years, (standard deviation 4.8 years, median 4.0 years).

The majority of pharmacy personnel 460 (86.8%) had each dispensed all three medicines (promethazine, Stopayne® and Goldgesic® syrups). All pharmacists had previously dispensed all the 3 syrups.

All pharmacy staff listed some correct indications for all syrups that they had dispensed. However, some personnel 37.8% (200) also listed off-license uses or totally incorrect indications for at least one of these medicines:

*Table I: Off-license/incorrect indications listed by personnel.*

Syrup	Off-license use/ Incorrect indication	Licensed use/ Correct indication
Promethazine	influenza, diarrhoea goosebumps, sedation	allergy, motion sickness/vomiting
Stopayne®	diarrhoea, colds, inflammation	relief of mild to moderate pain and fever
Goldgesic®	diarrhoea, colds, Inflammation	relief of mild to moderate pain and fever

Table I shows the correct indications/licensed uses and the incorrect indication/off-lisence uses of promethazine, Stopayne® and Goldgesic® by pharmacy personnel.

All participants (100%) indicated that parents come in and asked for these syrups for their children. Stopayne® was the most requested (n=48), followed by promethazine (n=43) and then Goldgesic® (n=28). Apart from the above stated indications (licensed and unlicensed), pharmacy personnel reported that parents were requesting these syrups for sedation.

*Table II: Pharmacy personnel who reported parent requests for syrups for sedation purpose in children.*

Syrup	n=530	(%)
Promethazine	110	20.8
Stopayne®	100	18.9
Goldgesic®	59	9.4

Table shows the requests that were made by parents/caregivers for the three syrups. Promethazine was the most requested by parents/caregivers from retail/community pharmacies.

All but 41 (7.74%) of the participants indicated that they counselled parents concerning the use of these medicines (92.45%). The counselling given was found to be in line with manufacturer literature (Package Inserts) as well as basic pharmacology, e.g., warning about drowsiness with all three syrups (273/530); constipation with Stopayne® and Goldgesic® (64/530).

The majority 476 (89.81%) of personnel were aware that these medicines have a recommended minimum age. However, fewer personnel stated the correct age, with Goldgesic® being the least known about medicine. 78 (41.05%) pharmacists were unable to state the correct age for each of the three medicines, whilst 243 (71.47) of the non-pharmacist personnel could not state the correct minimum age for all three.

Of the 476 personnel who stated that there is an age limit, 264 (55.46%) said that they dispense these medicines nevertheless for use in infants. Reasons for dispensing these syrups to infants include: the medicine being on a prescription (n=136); benefit outweighing risk in serious cases (n=36); there being no alternative medicine for the child's symptoms (n=27); and child approaching 2 years of age (n=18).

Chi-squared tests were performed to determine the significance of any association between certain categorical values, using p-value set at 0.05. A significant association was found between 'non-pharmacists' and 'not knowing the correct minimum age for Stopayne syrup' (p=0.03).

For those parents who had administered any of the three syrups to their babies (n=660), the follow observations were made as shown in Table III below

*Table III: The syrups which parents administered to their children.*

Syrup	Frequency	n (%)
Promethazine	271	22.05
Stopayne®	299	24.33
Goldgesic®	90	7.32
Had never administered any of the 3	569	46.30

Promethazine was administered mostly for allergies



(n=140), and also vomiting (n=60). Other uses were off-license for infants, i.e., cough and cold (n=30) or for a completely incorrect indication, i.e., fever (n=30). Stopayne<sup>®</sup> was given mostly for pain (n=15), as well as fever (n=11); allergies (n=8); sedation (n=26); coughs and colds (n=27); and stomach ache (n=17). Goldgesic<sup>®</sup> was given for pain (n=17) and stomach ache (n=31).

Off-license use of medicine or administration for inappropriate indication was found with 50% (330) of the parents who used these medicines. Furthermore, of the 660 parents who had administered at least one of these medicines to their children, 241 (36.52%) of them had children below two years of age.

Paracetamol syrup was the only other medication that parents reported having given to their children (n=303). Chi-squared tests revealed no association between any categorical values. Again, p-value was set at 0.05.

## Discussion

From the study, there was strong evidence to suggest high levels of inappropriate use of promethazine and promethazine-containing medicines in children less than three (3) years of age in Harare. This was indirectly portrayed by the lack of knowledge about the minimum age of administration of promethazine and promethazine-containing medicines (41.05% of pharmacists and 71.47% of other pharmacy personnel). More direct evidence was seen in the fact that more than half (55.46%) of the personnel who were aware that there is a minimum age, dispensed these medicines to parents in spite of this knowledge. Over-the-counter medicines such as those under investigation in this study might therefore be perceived by pharmacists as very safe for use, even in infants. The assertion by parents pharmacists and other pharmacy personnel that they give these syrups to children when the “benefit outweighs the risk”, showed that, any adverse effects of promethazine-containing medicines in children go largely uninvestigated or unreported in this country. Indeed, a literature search on this subject in Zimbabwe yielded no results.

Amongst the most cited reasons listed by pharmacy personnel for dispensing these medicines to infants in spite of there being a minimum age, was the drug being on a doctor's prescription. Unfortunately, from the data collected there was no way of determining whether any of these pharmacists ever queried such prescriptions with medical practitioners. If they generally did not query such prescriptions, then this was in line with doctor-pharmacist relationship studies that showed doctors had poor or little experience of pharmacists providing clinical advisory services to them (Bernstein *et al*, 1978; Paul *et al*, 2003; Nelson *et al*, 1978).

Another reason stated for dispensing promethazine-containing medicines for infants was a (real or perceived) lack of alternative medicines. Though not always available or affordable, there were indeed

alternatives. Some possible alternatives to promethazine were recommended as follows: vomiting should be ideally treated with anti-emetics only when the cause of vomiting is known, because anti-emetics may delay diagnosis of serious illness. Pharmacists should generally refer cases of vomiting lasting more than 24 hours, and not improving, to a doctor (Leung, 2007).

Airway congestion could be combated with OTC nasal saline (suitable for all ages). Coughs can be treated in children over 1 year of age with, medicines containing chlorpheniramine, dextromethorphan or codeine. However, products containing combinations of these drugs are no longer recommended for use in children under 6 years of age, with particular mention going to promethazine-codeine combinations (FDA Centre for Drug Evaluation and Safety, 2008). Anti-motility agents were not recommended for acute diarrhoea in young children (British National Formulary, 2007). Instead, acute diarrhoea, which is often caused by infection, should be left to run its course, administering oral rehydration salt solution to the infant. Referral to a medical doctor is necessary if diarrhoea for persists after 72 hours (Edwards, 1990).

An alternative to promethazine in the case of rashes caused by allergies might be chlorpheniramine (only for those children who are over 1 year of age). Topical corticosteroids such as hydrocortisone (an over the counter medicine at 0.1% strength) might also be applied in cases of allergic dermatitis.

The lack of knowledge in over a third of pharmacists was unexpected because of their years of training in basic and clinical pharmacology and therapeutics. This was perhaps, in part, due to a lack of pursuit of continuous education by practising pharmacists. Non-pharmacist personnel's lack of knowledge about the minimum age especially among pharmacy assistants was somewhat expected because of their lack basic training in pharmacology and drugs. Several studies supported the existence of such high levels of ignorance about drugs among pharmacy assistants (Mwakutuya, 2005).

## Conclusion

There was considerable inappropriate use of promethazine, Stopayne<sup>®</sup> and Goldgesic<sup>®</sup> syrups in children less than 3 years old in Harare. This was evidenced by the fact that 53.70% of interviewed parents were administering these syrups to children less than 2 years old. Also, of the parents who administered these syrups to their children about 7.7% (3/39) did so for sedation purposes.

## Recommendations

Training of all personnel who work in a pharmacy should be regulated and be made mandatory, in order to protect patients' health. The classification of

promethazine, Stopayne<sup>®</sup> and Goldgesic<sup>®</sup> syrups ought to be changed from pharmacy drugs to pharmacist-initiated medicines (PIM) or prescription preparation (PP). The potential risks of administration of promethazine to infants outweigh any possible therapeutic benefit and we therefore urge doctors, pharmacists, and parents to avoid its use in infancy.

### Acknowledgements

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